

**A comparison of several approaches for the analysis of a cluster randomised trial
with repeated measures**

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A cluster randomised trial (CRT) is a trial in which clusters of individuals, rather than individuals themselves, are randomised to different intervention groups [1]. In epidemiology, these trials are an important tool in the evaluation of nontherapeutic interventions including lifestyle modification or educational programs. These trials are usually designed with equal cluster sizes. In this study, we consider a cluster randomised trial with unequal cluster sizes; in which each subject is followed during several visits. The repeated observations (level 3) are nested within subjects (level 2) who are themselves nested within the unit of randomisation (level 1) [2].

For a CRT, two analyses can be made depending on whether or not the unit of analysis is the unit of randomisation, that is, a cluster-level analysis or an individual-level analysis. For the cluster-level analysis, with a binary outcome, one common approach is to use the average values of the event rates in each group. For the individual-level analysis, two models can be considered: a marginal model estimated by generalized estimating equations (GEE) and a random effects model. In this study, we compare GEE to different methods of maximum likelihood estimation of generalized linear mixed models: Gauss-Hermitte numerical quadrature, adaptive quadrature [3], penalized quasi-likelihood method, linearization methods and Monte Carlo EM algorithm. Therefore, since these models have two nested levels of clustering associated with cluster and subject, we consider a fixed-effects model, a two-level model and a three-level model. Type I error rates and standard errors are compared across the different statistical methods used for individual-level analysis. Finally, we confronted results obtained between the two types of analyses (cluster and individual),

A study of 1071 smokers from 61 general practitioners (GP) is used to illustrate the methods. This study was undertaken to examine whether a public health program based on a carefully adapted program of continuing education can increase tobacco cessation rates. The particular context due to a randomization of GP leads us to consider a CRT where each smoker is followed during 9 visits for up to one year. In this trial, the units of randomisation (GP) imply relatively small clusters with unequal size in two groups: median 26.6 vs. 15.9 in the intervention and control group respectively ($p=0.0001$). In this study, all models are significant results for the effect of intervention: for fixed-effect model OR=2.01 [1.76; 2.31], for two-level model (cluster random effect) OR=2.39 [1.65; 3.49] and for three-level model OR=2.37 [1.42; 3.94] (with adaptive quadrature). Appropriate adult learning training procedures based on behavioural and cognitive theories increased cessation counselling practice among GP. This had a significant impact on smoking cessation rates during several visits which illustrate the dynamic of tobacco cessation.

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[3] Rabe-Hesketh and Skrondal. Multilevel and Longitudinal Modeling Using Stata. Stata Press. 2005